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RECENT ADVANCES ON THE SYNTHESIS OF PIPERIDINES THROUGH RUTHENIUM-CATALYZED RING-CLOSING METATHESIS (RCM) REACTIONS

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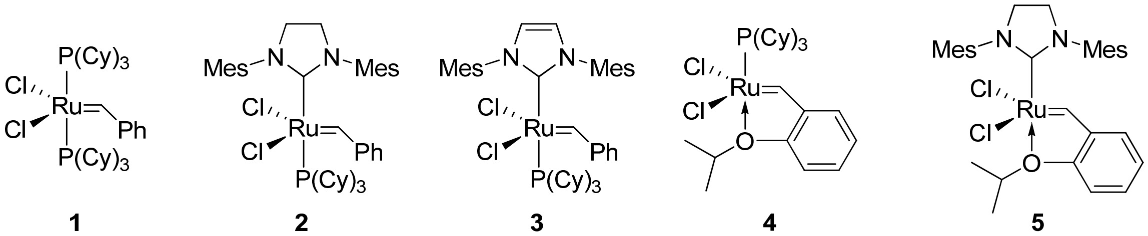
Abstract – Ring-closing metathesis reactions of dialkenyl amines, amides and carbamates catalyzed by Ru-catalysts provide efficient approaches to six-membered nitrogen heterocyclic compounds, which are precursors of a variety of natural products and related compounds.

CONTENTS

1. INTRODUCTION

The presentation of Nobel Prize to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock “*for the development of the metathesis method*”, recognized the influence and power of the metathesis reactions in Organic Synthesis.[1] Several stable, functional group tolerant and commercially available catalysts have been reported for metathesis reactions,[2] the most common utilized being Ru-based catalysts **1-5** although a portfolio of modified catalysts[3-5] is now available from several chemical suppliers.



1 Grubbs I

2 Grubbs II

3 Grubbs-Nolan

4 Hoveyda-Grubbs I

5 Hoveyda-Grubbs II

Figure 1

These catalysts have been successfully employed in many instances for the construction of small molecules and total syntheses of natural products.[6,7] A variety of metathesis reactions are known,[8-10] including ring-closing, ring-opening, ring-expansion, domino, enyne,[11,12] polymerization[13] and cross-metatheses.[14-17] From these reactions ring-closing metathesis (RCM) reactions have gained a prominent position in the past decades as a useful class of reactions for constructing both carbo- and heterocycles.[18] Due to the extreme importance of RCM reactions and related processes there have been several reviews on this topic to date.[19-25]

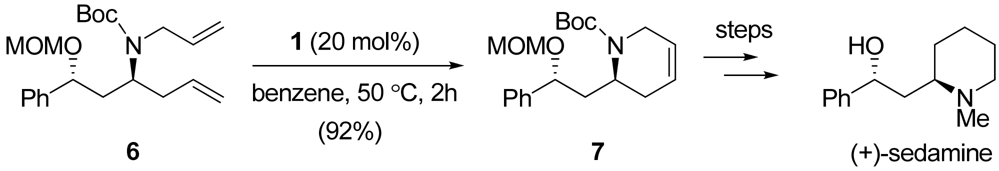
The metathesis reactions have a wide functional groups tolerance, although in some instance the presence of a basic nitrogen or a primary amine can affect the yield of the reaction.[26,27] Because of this reason the metathesis reactions with nitrogenated compounds have been studied in detail[28] and, in particular, RCM reactions of nitrogen-containing compounds directed to the synthesis of alkaloids, peptidomimetics and other compounds have been recently considered.[29] In this respect, an excellent compilation of approaches for synthesizing pyrrolidine and piperidine natural alkaloids using RCM reactions as a key step has been reported in 2003 by Lebreton and Felpin.[30]

This review focuses on recent developments of RCM reactions on nitrogen-containing substrates leading to the synthesis of nitrogenated six-membered rings of synthetic and biological importance and covers the literature from January 2003 to April 2011.

2. SYNTHESIS OF SINGLE-RING TETRAHYDROPIPERIDINES

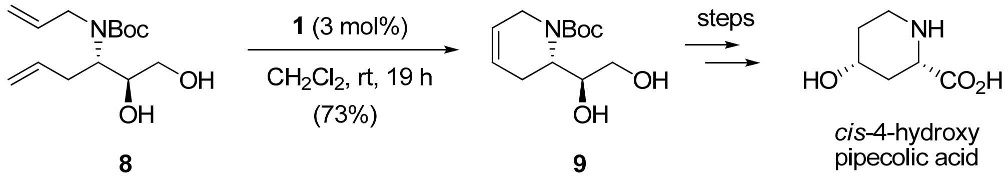
2.1. SYNTHESIS OF *N*-CARBAMOYL TETRAHYDROPYRIDINES

The piperidine alkaloid (+)-sedamine has been prepared from *N*-Boc protected dialkenylamine **6** using RCM as a key reaction. The metathesis reaction was promoted by Grubbs I catalyst **1** (20 mol%) and took place in good chemical yield at 50 °C for 2 h (Scheme 1).[31]



Scheme 1

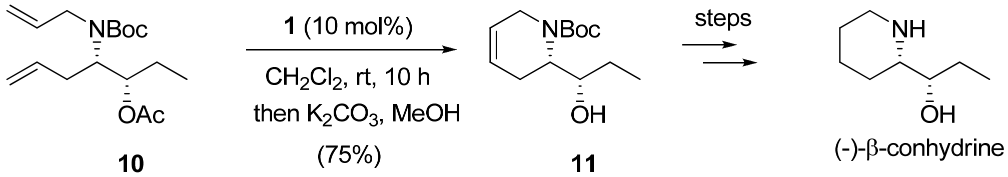
The reaction showed a good compatibility with acid-sensitive protecting groups and it could be carried out at room temperature, although 24 h were needed for completing the reaction.[32] The reaction conditions have shown to be tolerant with free hydroxyl groups[33] allowing an expeditious synthesis of *cis*-4-hydroxypipecolic acid (Scheme 2).[34] In order to achieve a good conversion it was needed to add the catalyst again (3 mol%) after the first 4 h of reaction. A similar approach was used for preparing 3-hydroxypipecolic acid.[35]



Scheme 2

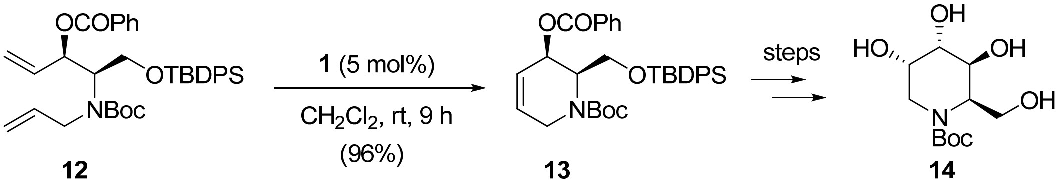
In general, *N*-Boc dialkenylamines afforded excellent results in RCM reactions catalyzed by **1**. Depending on the substrates the reaction can be carried out in different solvents at several temperatures. The ligand core of (-)-sparteine has been constructed by RCM of a *N*-Boc dialkenylamine in dichloromethane at room temprature, the product being obtained in essentially quantitative yield.[36]

By carrying out the reaction in dichloromethane at room temperature for 10 h the intermediate precursor of (-)-β-conhydrine was obtained from compound **10** (Scheme 3).[37,38] This alkaloid has also been prepared by other routes involving RCM reactions of *N*-Boc dialkenylamines catalyzed by **1**. In all cases a high compatibility with hydroxyl protecting groups including acetals,[39] silyl[40] and benzyl ethers,[41] and acetonide groups was observed.[41] In the latter case, the approach was extended to the preparation of indolizidine (-)-lentiginosine.



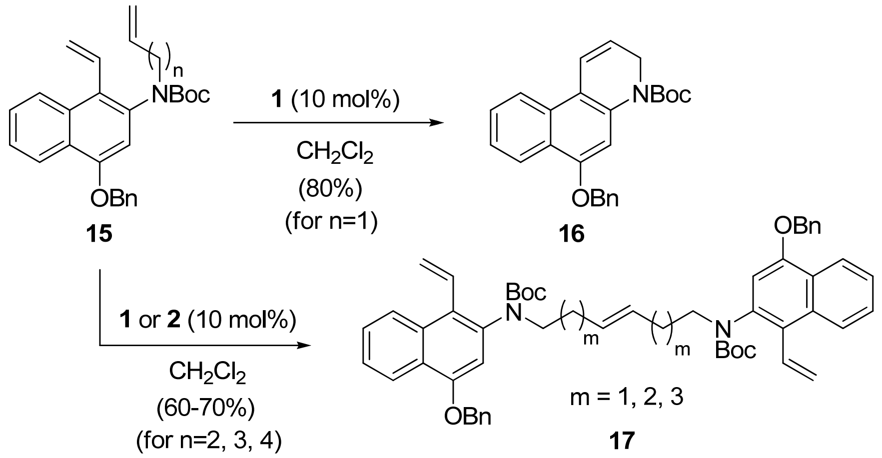
Scheme 3

Enantiomeric (+)-β-conhydrine was also synthetized from the enantiomer of **11** by using the same reaction conditions illustrated in Scheme 3.[41] By using this strategy and under similar reaction conditions, a general methodology for preparing 2-substituted-3-hydroxypiperidines was developed.[42] RCM reactions of hydroxylated *N*-Boc dialkenylamines has been successfully employed in the preparation of azasugars such as 1-deoxygulonojirimycin **14** (Scheme 4).[43]



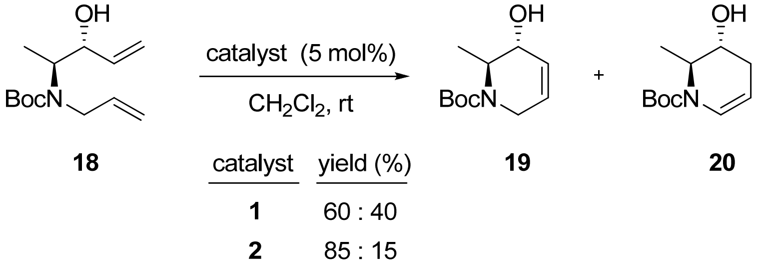
Scheme 4

Catalyst **1** was also employed with aromatic *N*-Boc alkenylamines such as **15**. By using 10 mol% of catalyst, tricyclic derivative **16** was obtained in good chemical yield (Scheme 5).[44] In the case of extended dienes **15** (n= 2, 3, 4) only dimerization products **17** were obtained instead the corresponding expanded ring. The same results were observed with Grubbs II catalyst **2**.



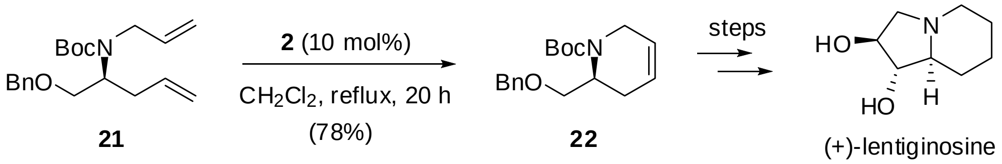
Scheme 5

In some instance side reactions affording isomeric enamines have been observed. RCM of **18** catalyzed by **1** afforded a 60:40 mixture of compounds **19** and **20**. This ratio was changed to 85:15 by using Grubbs II **2** as a catalyst under the same reaction conditions (Scheme 6).[45]



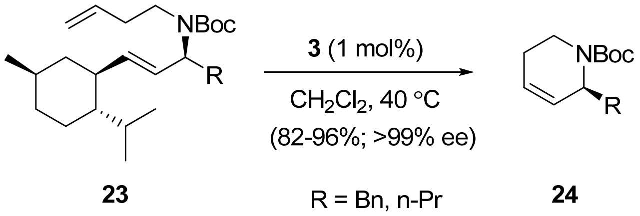
Scheme 6

Catalyst **2** has been successfully employed in RCM reactions of fluorinated dialkenyl *N*-Boc amines[46] and in the synthesis of the alkaloid (+)-lentiginosine from **21** (Scheme 7).[47] In both cases the reaction was carried out with 10 mol% of catalyst in dichloromethane at reflux.



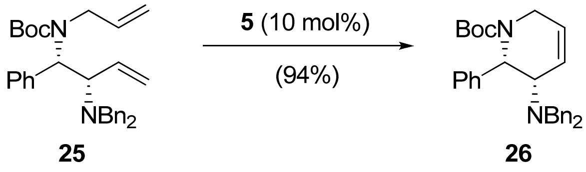
Scheme 7

Alternatively, catalyst **3** led also to good results quite similar to those observed with catalyst **1**, with *N*-Boc dialkenyl derivatives in dichloromethane (or dichloroethane) at reflux.[48] By using 1 mol% of **3** and a chiral auxiliary, enantiomerically pure *N*-Boc tetrahydropyridines **24** were readily prepared in high chemical yields and enantioselectivities (Scheme 8).[49]



Scheme 8

The methodology illustrated in Scheme 8 was applied to the synthesis of the alkaloid (+)-lentiginosine.[50] Substrates bearing nucleohilic amine functions such as **25** are also amenable of being used as substrates in RCM reactions by employing Hoveyda-Grubbs II catalyst **5** (Scheme 9).[51] Compound **26** is a precursor of the potent neurokinin P receptor antagonist (+)-(2*S*,3*S*)-CP-99,994. The same strategy was used for preparing epimeric (-)-(2*S*,3*R*)-CP-99,994.[52]

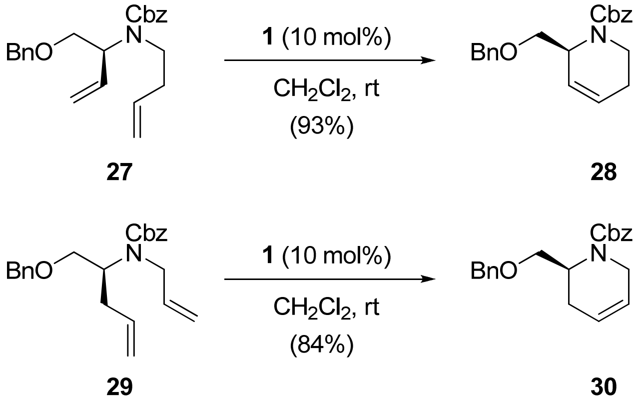


Scheme 9

Catalyst **5** was also employed with *N*-Boc dialkenyl substituted substrates in combination with a N-H insertion reaction. The resulting tandem protocol was used for the preparation of saturated nitrogen heterocycles.[53]

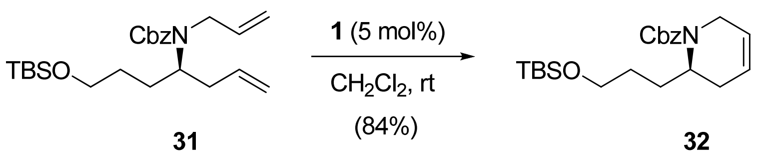
In a similar way to *N*-Boc protected substrates, dialkenylamines protected as *N*-Cbz carbamates underwent RCM reaction with Grubbs catalysts **1** and **2**. Compounds **27** and **29** afforded the corresponding tetrahydropyridines **28** and **30**, respectively in excellent chemical yields upon treatment with 10 mol% of **1** in dichloromethane at room temperature (Scheme 10).[54] The reaction was also extended to the formation of

5- and 7-membered nitrogen heterocycles and further used in the synthesis of iminosugars. The reaction proceeded smoothly with substituted alkenes and in the presence of a siloxygroup. In this case, however, reflux was needed for completing the reaction.[38]



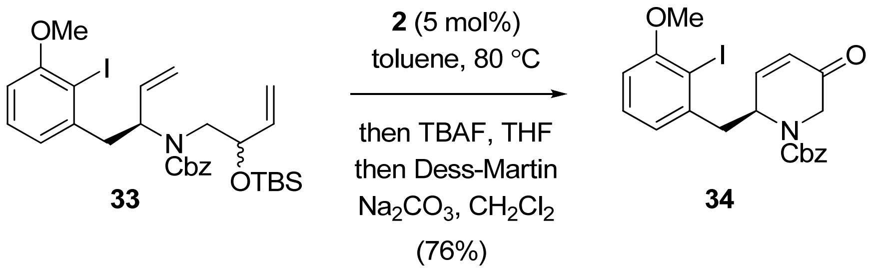
Scheme 10

By using similar strategies to those illustrated with *N*-Boc carbamates, 3-hydroxypipecolic acids have been accessed from *N*-Cbz dialkenyl amines employing catalyst **1**.[55] When the reaction was carried out with unsusbtituted alkenes dichloromethane was used as a solvent at room temperature.[56]A versatile enantioselective synthesis of the marine alkaloids barrenazines was accomplished through RCM of **31** catalyzed by **1** as a key step (Scheme 11).[57]



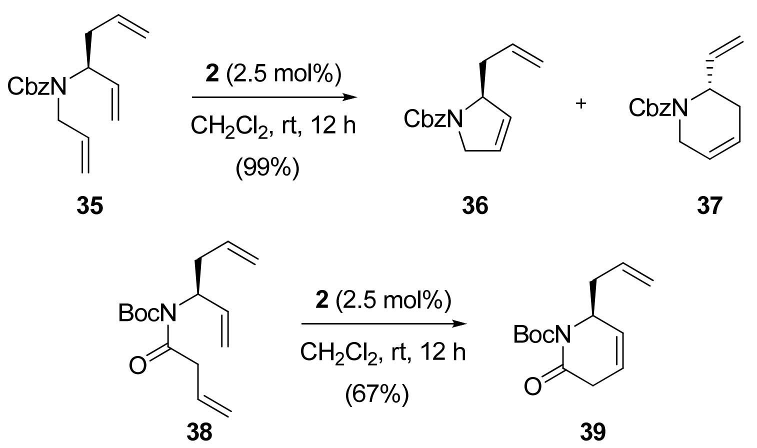
Scheme 11

The formal synthesis (-)-haouamine A was achieved from intermediate **34** readily obtained from precursor **33** through RCM catalyzed by **2** and *in situ* deprotection and oxidation (Scheme 12).[58]



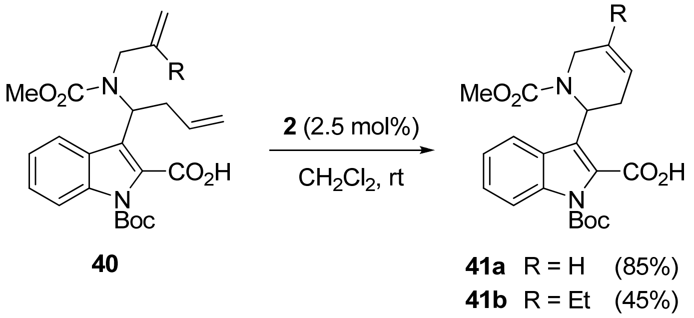
Scheme 12

The presence of a third alkene in the molecule led to both five- and six-membered products as in the case of **35** which on treatment with 2.5 mol% of **2** afforded a 43:57 mixture of pyrroline **36** and tetrahydropyridine **37**. In contrast, alkenyl amide **38** only cyclized, under the same reaction conditions, to the corresponding lactam **39** (Scheme 13).[59]



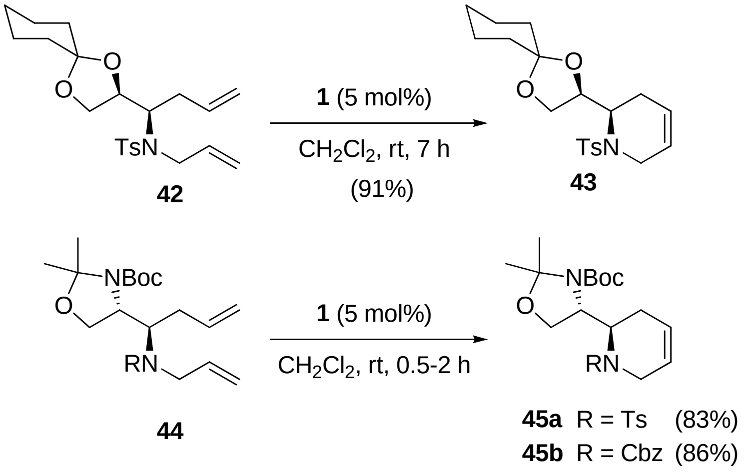
Scheme 13

The RCM of dialkenyl *N*-methoxycarbonyl derivative **40** took place in 85% yield with catalyst **2** (Scheme 14).[60] Interestingly, the reaction was carried out in the presence of a free carboxylic acid and it was applied to a substituted substrate even though lower yield was observed in that case.[61] Dialkylidene urea derivatives were also used as substrates in RCM reactions with **1** as a catalyst.[62]



Scheme 14

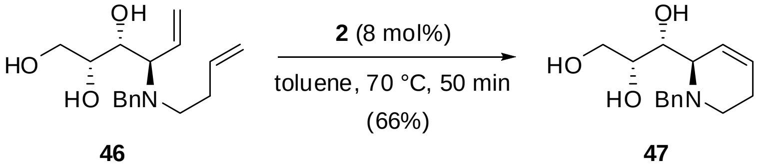
N-Tosyl dialkenyl amine **42** afforded the corresponding tetrahydropyridine **43** upon treatment with catalyst **1** in dichloromethane at room temperature.[63] The same reaction was achieved with compound **44** showing a good compatibility with the more labile *N*,*O*-acetonide group (Scheme 15).[64]



Scheme 15

2.2. SYNTHESIS OF *N*-BENZYL TETRAHYDROPYRIDINES

The above mentioned RCM reactions with carbamates, leading to similar results,[65] involved protection of the nitrogen atom in such a way that it cannot act as a nucleophile; nevertheless it was possible to carry out RCM reactions in the presence of a dibenzylamino group[51,52] and *N*-benzyl dialkenyl amine **46** underwent RCM in the presence of catalyst **2** (Scheme 16).[66] Notably, the reaction took place in the presence of unprotected hydroxyl groups. The procedure was also extended to the formation of pyrrolines.



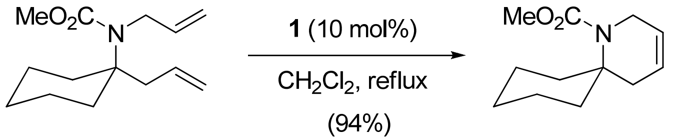
46 **47**

Scheme 16

RCM reactions of *N*-benzyl dialkenylamines have also been reported employing **1** as catalyst in refluxing benzene with sugar-derived substrates en route to trihydroxy-quinolizidine analogues.[67]

2.3. SYNTHESIS OF SPIRO TETRAHYDROPYRIDINES

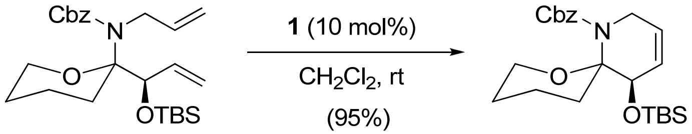
Of particular interest is the application of the above discussed reactions in the synthesis of spiro derivatives which are difficult to prepare by other routes. RCM reaction of cyclohexyl derivative **48** afforded spirocompound **49** in excellent yield (Scheme 17).[68]



48 **49**

Scheme 17

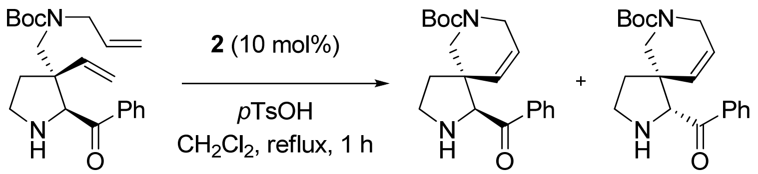
Several oxo-indolespirocyclic derivatives that resulted to be potent inhibitors of HIV protease have been prepared through RCM catalyzed by **1**.[69] Spirocyclic reverse turn mimics were accessed through a higly practical RCM strategy based on the use of catalyst **2** and solid-phase synthesis techniques.[70] Spiroketal related natural products were synthesized through a ketal-tethered RCM strategy. Among those products spiroaminal **51** was obtained from **50** through RCM reaction promoted by **1**.[71]



50 **51**

Scheme 18

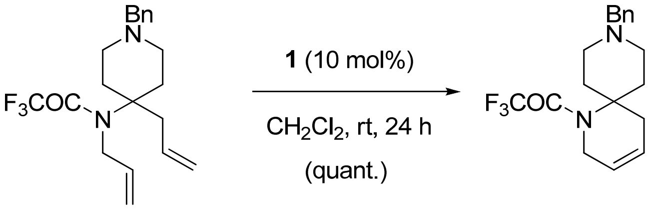
RCM reaction of **52** catalyzed by **2** and in the presence of p-TsOH afforded a 3:1 mixture of spirocycle **53** and epimer **54**, probably as a consequence of the high acidity of the C-2 proton (Scheme 19).[72] This methodology was also applied to larger heterocyclic rings. RCM reactions catalyzed by **2** in the presence of p-TsOH have been reported for preparing not only tetrahydropyridines but also pyrrolines and larger rings.[73]



52 **53** **54**

Scheme 19

Spirocyclic compounds related to the bioactive natural products histrionicotoxins were synthesized using RCM as a key step. As an example, compound **56** was obtained from trifluoroacetamide **55** by treatment with **1** in dichloromethane at room temperature. In spite of the presence of a NBn group the reaction took place in quantitative yield (Scheme 20).[74]

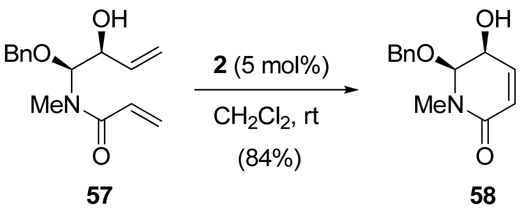


55 **56**

Scheme 20

2.4. SYNTHESIS OF DIHYDROPYRIDIN-2(3*H*)-ONES

N-Alkenyl acrylamides have been used as suitable starting materials for obtaining six-membered lactams through RCM reactions. Treatment of **57** with catalytic **2** in dichloromethane at room temperature afforded unsaturated lactam **58** in good yield (Scheme 21).[75]

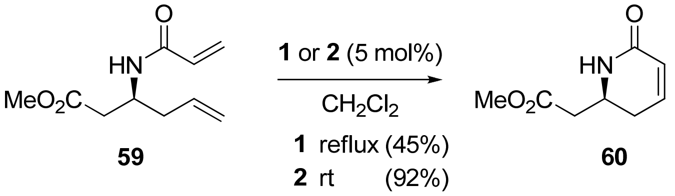


57 **58**

Scheme 21

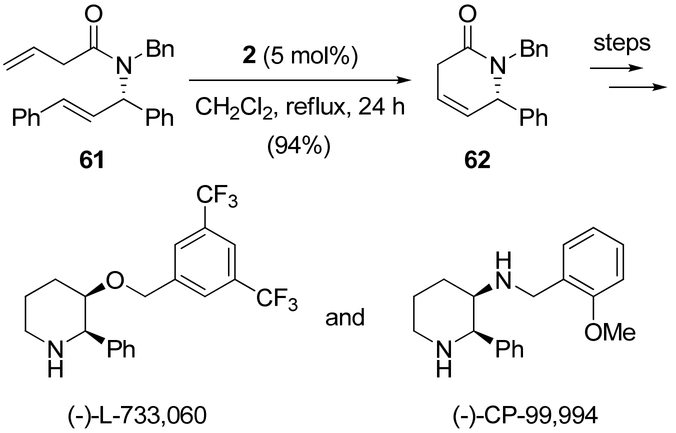
With lower catalyst loading (4-5 mol%) reflux was necessary[76] but good yields were obtained not only for tetrahydropyridines but also for five- and seven-membered rings.[73] Similar results were obtained with Grubbs I catalyst **1**[77] and *N*-(2,4-dimethoxybenzyl) derivatives.[78] On the other hand, very similar reactions has also been described at room temperature by using 7.5 mol%[60] and 2.7 mol%[59] of catalyst **2**.

Some differences in reactivity have been observed between Grubbs' catalysts **1** and **2**. While alkenyl acrylamide **59** cyclized readily in the presence of **2** at room temperature, with **1** as a catalyst the reaction did not work as well and 45% yield of **60** was obtained after several hours at reflux.[79]



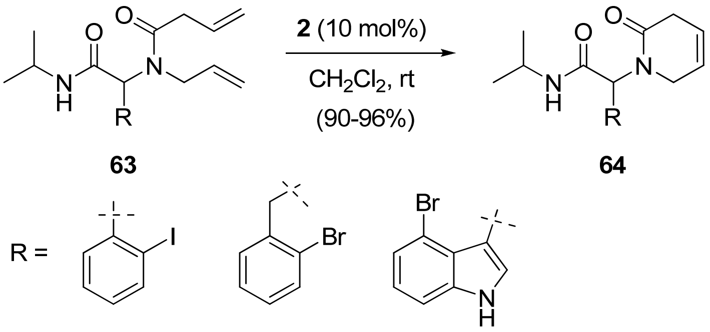
Scheme 22

The reaction has also been carried out with substituted alkenes but 24 h at reflux were needed for completing the reaction (Scheme 23). Lactam **62** served as an immediate precursor for the synthesis of (-)-CP-99,994 and (-)-L-733,060, two piperidine analogues with high affinity and selectivity with human NKI receptor.[80]



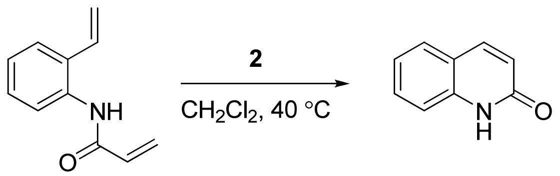
Scheme 23

A series of six-membered lactams have been prepared by RCM reaction catalyzed with **2** in excellent yields. The obtained compounds were used in the preparation of novel bridged bicyclic lactams showing various degrees of pyramidalization of the bridgehead nitrogen atom (Scheme 24).[81]



Scheme 24

N-Phenylacrylamide **65** underwent RCM reaction in the presence of **2** (10 mol%) to provide **66** in excellent yield (Scheme 25). Interestingly, the catalyst loading could be reduced to 5 mol% and 2 mol% without loss of efficiency although longer reaction times were needed.[82]



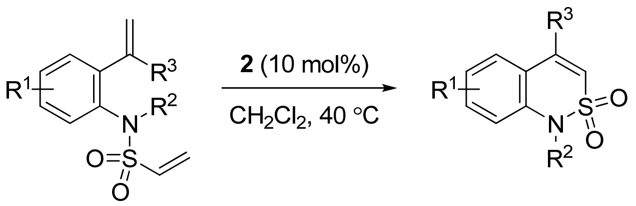
65 **66**

catalyst	t (h)	yield (%)
10 mol%	2.5	95
5 mol%	7.5	88
2 mol%	96	91

Scheme 25

When the reaction was carried out with substituted alkenes good results were obtained by using 5 mol% of catalyst with the exception of substrates bearing either bulky substituents in the double bond directly linked to the aromatic ring or halogenated substituents at the acrylamide moiety.[82]

In the case of *N*-phenylethylenesulfonamides an important solvent effect was observed, whereas no reaction was observed in benzene, good yields were obtained for the reaction carried out in dichloromethane (Scheme 26).[82]



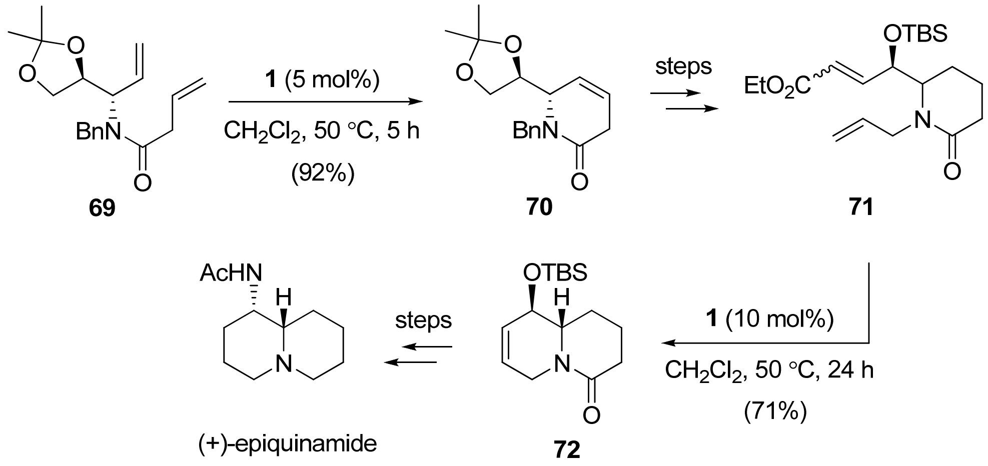
67 **68**

R^1	R^2	R^3	yield (%)
2-Me	H	H	87
4-Me	H	H	95
2-Cl	H	H	82
4-OMe	H	H	100
4-CF_3	H	H	85
2,4-diCl	H	H	75
H	H	H	100
H	Me	H	86
H	Bn	H	85
H	4-CNBn	H	82
H	4-BrBn	H	96
H	4-CF_3Bn	H	94
H	H	Me	92

Scheme 26

Two RCM reactions have been used in a reaction sequence leading to (+)-epiquinamide starting with dialkenyl amide **69**, which furnished *N*-benzyl-1,6-dihydropyridin-2(3*H*)-one **70**. After several steps a second RCM reaction on **71** allowed preparation of bicyclic lactam **72**, precursor of the target compound. Catalyst **1** was used in both reactions under the same reaction conditions. Nevertheless, whereas RCM of **69** needed 5 mol% of **1** and 5h of reaction, the second metathesis on a reaction substituted substrate finished in

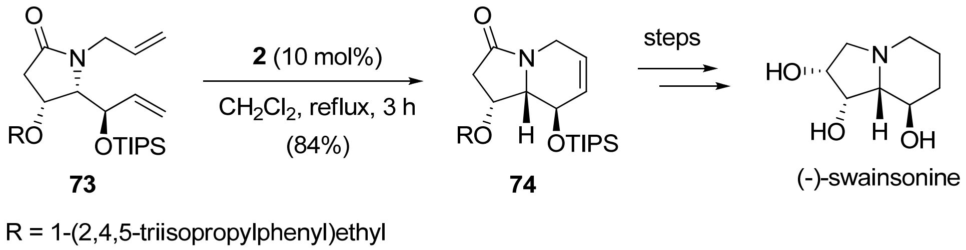
24 h by using 10 mol% of **1** (Scheme 27).[83]



Scheme 27

3. SYNTHESIS OF BICYCLIC COMPOUNDS

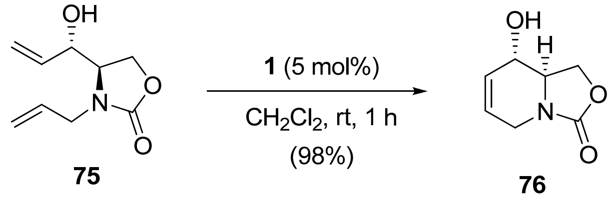
The synthesis of bicyclic lactams by RCM of acrylamides or *N*-alkenylamides has been widely employed as a very convenient approach to a variety of bi- and polycyclic alkaloids and related compounds. As an example, RCM of **73** catalyzed by **2** was efficiently achieved in refluxing dichloromethane to afford bicycle **74**, which was further used in the synthesis of (-)-swainsonine (Scheme 28).[84] The RCM reaction of this sort of compounds have also been employed as a part of several sequential processes directed to the preparation of different heterocyclic scaffolds.[85]



Scheme 28

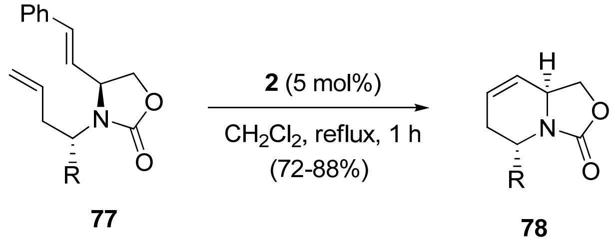
This approach based on RCM of *N*-allyl-δ-lactams was employed for preparing several indolizidine alkaloids including (-)-2-epilentiginosine,[86] castanospermine derivatives[87] and other polyhdroxylated analogues.[88] The approach is also valid for *N*-acryloylpiperidines leading to the same indolizidine skeleton by formation of the five-membered ring.[89] Similar results were obtained with **1** as a catalyst; although longer times of reaction were required, the chemical yield was excellent.[90] The methodology is also applicable to the synthesis of dihydro-1*H*-pyrrolizin-3(2*H*)-ones and expanded tetrahydro-1*H*-pyrrolo[1,2-*a*]azepin-3(2*H*)-ones.[91]

Cyclization of *N*-allyloxazolidinone **75** catalyzed by **1** took place smoothly at room temperature providing bicyclic compound **76** in excellent yield (Scheme 29).[92] Compound **76** was further converted into the alkaloids deoxymannojirimycin and swainsonine.



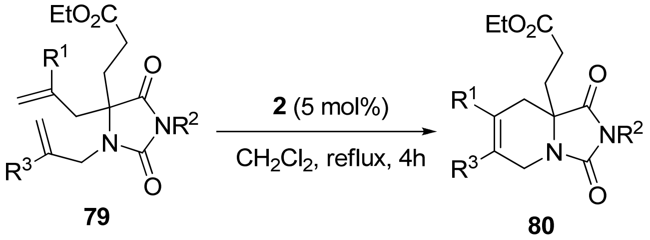
Scheme 29

The reaction of *N*-homoallyloxazolidinone **77** bearing a phenyl-substituted alkene catalyzed by **2** was carried out under reflux and a good chemical yield was obtained after 1 h. (Scheme 30).[93]



R = Et, *n*-Pr, *n*-Bu, C_7H_{15}, $C_{11}H_{23}$

Scheme 30

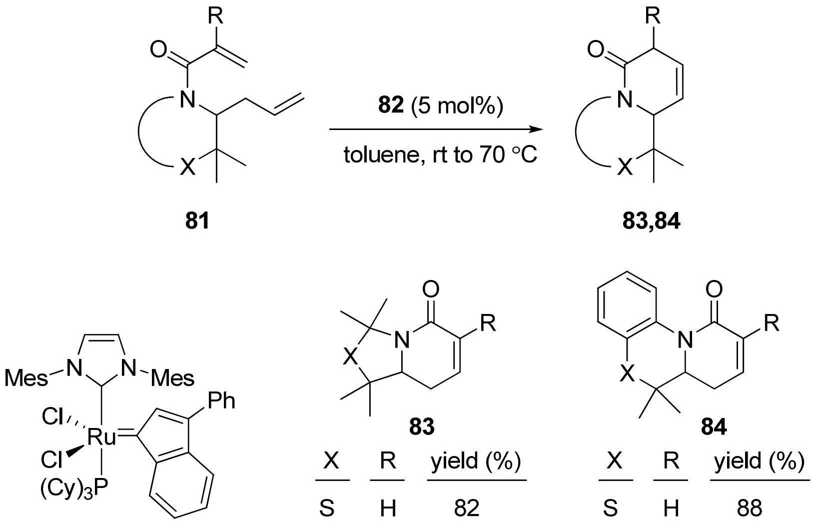


R^1	R^2	R^3	yield (%)
H	*n*-Pr	H	93
H	Ph	H	88
H	Bn	Cl	75
H	Ph	Me	79
H	Bn	$ClCH_2$	85
H	Bn	CO_2Et	55
Cl	*n*-Pr	H	77
Me	*n*-Pr	H	86

Scheme 31

In the case of phenyl-substituted alkenes similar results have been reported with **1**.[94] The same approach based on RCM of a phenyl-substituted *N*-alkenyloxazolidinone served for preparing the C_{10}-C_{24} fragment of (+)-cannabisativine.[95] In this case the reaction was catalyzed by **2** in refluxing dichloromethane and 88% yield was obtained. In a similar way, RCM on *N*-allylhydantoins **79** provided the corrresponding bicyclic structures **80** in good yield. The reaction worked well on a variety of substrates with different substituents on the double bonds thus providing a good versatility and the possibility of further functionalization (Scheme 31).[96]

Catalyst **82**, similar to Grubbs II catalyst **2** was used for the synthesis of lactams **83** and **84** through RCM of acrylamides **81**. The reaction was started at room temperature with a slow increase of temperature up to 70 °C. By using 5 mol% of catalyst, the reaction proceeded in good yield in several hours. The versatility of the reaction was well-demonstrates through the preparation of thiazolidine-, ozaxolidine-, benzothiazine and benzoxazine-fused lactams (Scheme 32).[97]



81

83,84

82

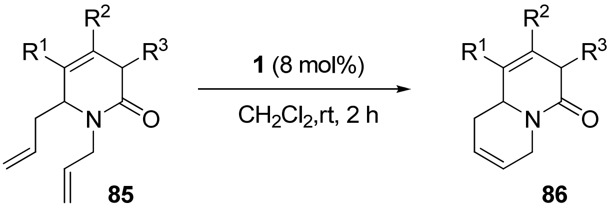
83

X	R	yield (%)
S	H	82
S	Me	80
O	H	65
O	Me	85

84

X	R	yield (%)
S	H	88
S	Me	77
O	H	56
O	Me	76

Scheme 32



85

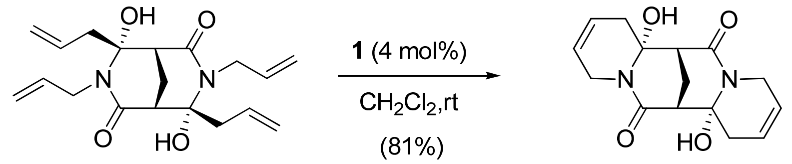
86

R^1	R^2	R^3	yield (%)
H	H	H	83
H	H	Me (trans)	82
H	H	Me (cis)	76
H	Me	H	75
Me	H	H	75
H	H	Bn (trans)	87
H	H	Bn (cis)	88

Scheme 33

The quinolizidine ring system was conveniently approached by RCM reaction of dialkenyldihydropyridin-2-ones **85**, catalyzed by **1** (Scheme 33). The reaction proceeded smoothly at room temperature for 2 h by using 8 mol% of catalyst.[98] The reaction also proceeded well with 5 mol% of catalyst except in the case of susbtituted alkenes that required refluxing toluene for achieving a moderate yield.[99] Good results were also obtained by using **2** as a catalyst even with low catalyst loadings (1.4 mol%).[100]

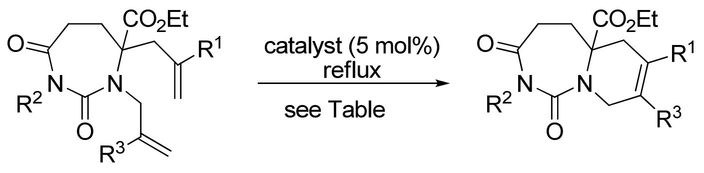
A two-directional approach to sparteine derivatives employed RCM reaction of dialkenylbispidine **87** as a key step. The tetracyclic derivative **88** was formed in good yield upon treatment with 4 mol% of **1** in dichloromethane at room temperature (Scheme 34).[101]



87 **88**

Scheme 34

A series of 1,3-dioxo-tetrahydropyrido[1,2-*c*][1,3]-diazepines **90** with different substituents have been prepared by employing different catalysts and reaction conditions. In all cases good results were obtained (Scheme 35).[102]

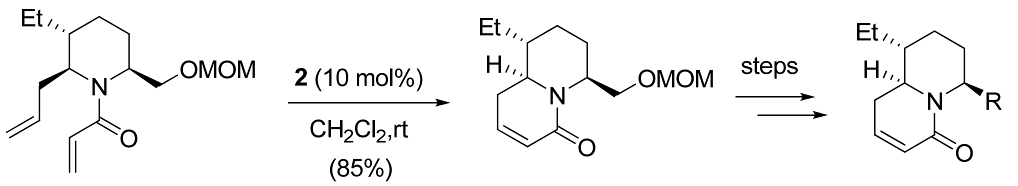


89 **90**

R^1	R^2	R^3	catalyst	solvent	time (h)	yield (%)
H	*n*-Pr	H	**2**	CH_2Cl_2	2	93
H	Ph	H	**2**	CH_2Cl_2	2	88
H	Bn	Cl	**2**	benzene	14	75
H	Ph	Me	**2**	CH_2Cl_2	2	79
H	Bn	$ClCH_2$	**2**	CH_2Cl_2	2	85
H	Bn	CO_2Et	**5**	CH_2Cl_2	2	55
Cl	*n*-Pr	H	**2**	benzene	14	77
Me	*n*-Pr	H	**2**	CH_2Cl_2	2	86

Scheme 35

N-Acryloyl-2-allylpiepridines **91** gave access to various compounds of biological interest. Among them, posion-frog alkaloids 233A, 235U and 251A were synthesized by using RCM of **91** as a key step (Scheme 36).[103]

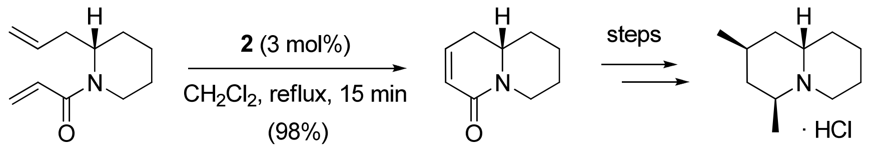


91 **92**

233 A R = $HC{\equiv}C(CH_2)_3$
235 U R = $H_2C{=}CH(CH_2)_3$
251 A R = C_6H_{13}

Scheme 36

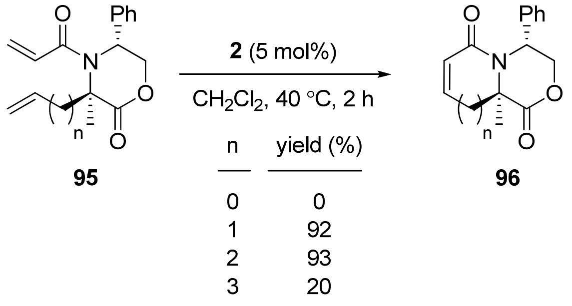
The same type of substrate was employed in the preparation of a series of piperidines investigated as opioid receptor antagonists,[104] for the asymmetric synthesis of cernuane-type *Lycopodium* alkaloids[105,106] and for preparing novel polyhydroxylated quinolizidines with glycosidase inhibitory activity.[107] The natural quinolizidine alkaloid (+)-cermizine C has been recently prepared through a highly efficient RCM of acrylamide **93** and further functional group transformation (Scheme 37).[108]



93 **94** (+)-cermizine C

Scheme 37

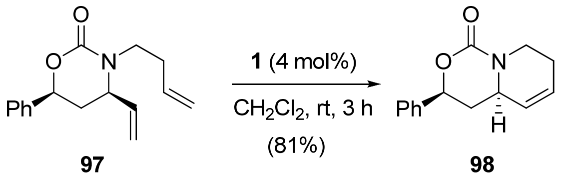
With acrylamides **95** the reaction only proceeded satisfactorily in the case of six- and seven-membered rings to give compounds **96** (n=1, 2) probably due to the steric hindrance of the corresponding precursor of the five-membered derivative **96** (n=0). Similarly, the presence of a quaternary center can affect the reaction as demonstrated by the low yield obtained in the formation of the eight-membered compound **96** (n=3) (Scheme 38).[109]



n	yield (%)
0	0
1	92
2	93
3	20

Scheme 38

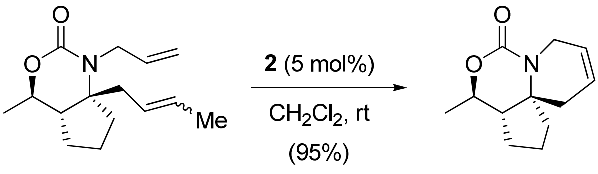
N-Homoallyl cyclic carbamate **97** underwent RCM upon treatment with 4 mol% of **1** to provide bicycle **98** in good yield. The reaction proceeded smoothly in dichloromethane at room temperature (Scheme 39).[110]



97 **98**

Scheme 39

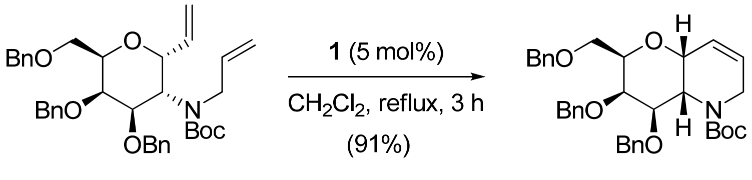
Similarly, treatment of diene **99** with 5 mol% of Grubbs II **2** afforded tricyclic derivative **100**, having a 6-azaspiro[4,5]decane skeleton, in high yield (Scheme 40).[111]



99 **100**

Scheme 40

Bicyclic structures were also accessible from dialkenylcarbamates like **101**. Treatment of this compound with **1** (5 mol%) provided bicyclic derivative **102** in very good yield. The reaction was also applied to an epimer as well as to an azepine derivative (Scheme 41).[112]

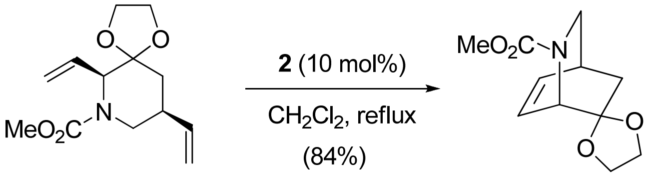


101 **102**

Scheme 41

The obtained compounds were further converted into azasugar analogues that showed inhibitory activity towards α-glycosidases at mM concentration. The same approach was employed for preparing carbohydrate-derived hybrids with 1-deoxynojirimycin which showed to be biologically active towards α-glucosidase and β-galactosidase.[113] Sugar-fused piperidines have been prepared by the RCM-based methodology illustrated in Scheme 41 and further used as key precursors of deoxyazasugars.[114]

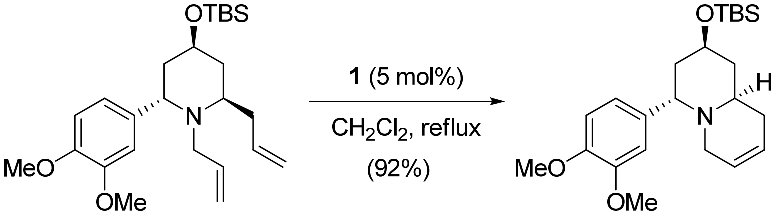
Isoquinuclidine **104** was obtained in good yield through RCM of divinylpiperidine **103**. In spite of the unfavourable boat conformation required to bring the substituents at positions 2- and 5- into the axial orientation needed for the RCM, the reaction proceeded smoothly with **2** in refluxing dichloromethane (Scheme 42).[115] Compound **104** was further used as a key intermediate in the synthesis of the alkaloid (+)-cantharanthine.



103 **104**

Scheme 42

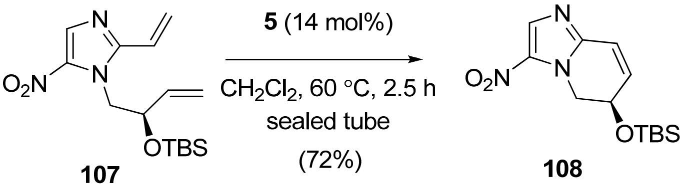
The 1,3-bis(allyl)piperidine **105** underwent RCM in the presence of catalytic **1** to give **106**, an immediate precursor of the alkaloid (-)-lasubine (Scheme 43).[116]



105 **106**

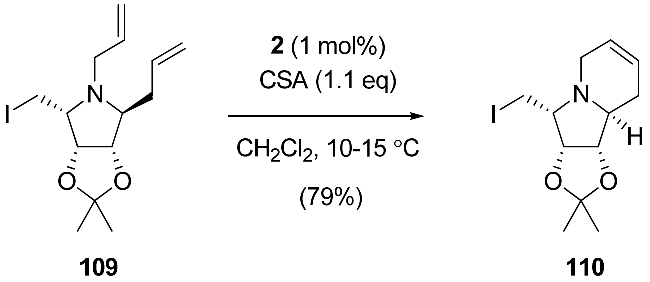
Scheme 43

Although several examples can be found in the literature concerning compatibility of free hydroxyl groups with the ruthenium-catalyzed RCM reaction,[33,34,45,65,74,92] TBS protection was required in the case of compound **107** to avoid undesired elimination. The reaction was catalyzed with catalyst **5** and it was carried out in a sealed tube for 2.5 h at 60 °C (Scheme 44).[117] A similar derivative was also subjected to RCM with the same catalyst and 15 h at 55 °C were needed for completing the reaction.



Scheme 44

The indolizidine ring has also been accessed through RCM reactions from substrates with basic nitrogen atoms. Enantiomerically pure polyhydroxylate indolizidines were prepared starting from dialkenyl sugars like **109** (Scheme 45).

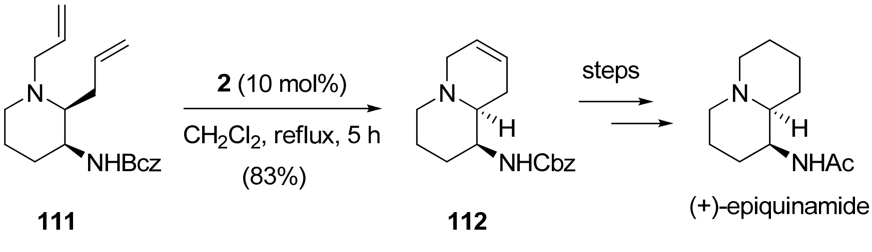


Scheme 45

In spite that free amines do not tolerate completely the RCM reaction due to deactivation of the catalyst by basic nitrogen, the catalyst **2** is compatible with the presence of ammonium salts.[118] Accordingly, RCM of **109** in the presence of camphorsulfonic acid (CSA) using 1 mol% of **2** proceeded successfully to afford bicyclic derivative **110**.

The reaction was kept cold (10-15 °C) to avoid the obtention of a quinolizidine as a result of the formation of an intermediate aziridinium ion (resulted from an intramolecular substitution of the primary iodide by the nitrogen atom) and further ring opening by attack of the iodide counterion.[119]

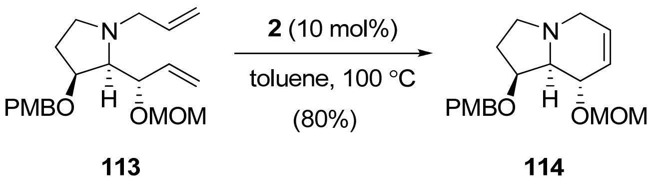
The use of a basic *N*-allyl group in RCM reactions in the absence of any acid is exemplified by the reaction of **111** catalyzed by **2**, which furnished the corresponding bicyclic derivative **112** in good yield. Compound **112** was used for preparing the alkaloid (+)-epiquinamide (Scheme 46).[120]



Scheme 46

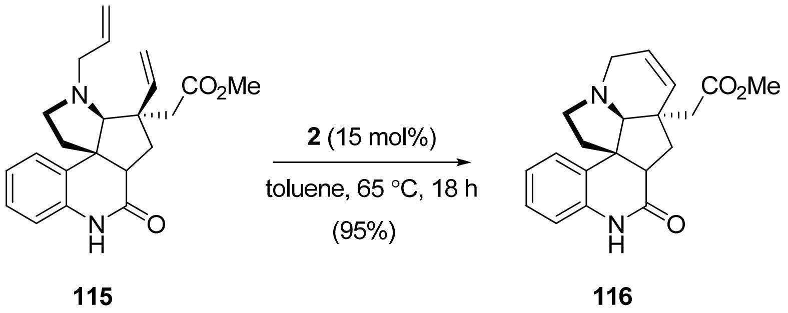
RCM of *N*-allyliminosugars has been used as a key step in the synthesis of various indolizidine skeletons including 8-*epi*-swainsonine. Similar approaches using both Grubbs I **1**[121] and Grubbs II **2**[122] have been reported. For the latter, the catalyst was added in two separate portions over 24 h in order to complete the reaction.[123]

N-Allylpyrrolidine **113** provided bicycle **114** upon treatment with catalyst **2** in two portions of 10 mol% of catalyst over 4 h. The reaction was carried out in toluene at 100 °C to achieve 80% yield (Scheme 47).[124] Compound **114** was used as a precursor of (+)-6-*epi*-castanospermine.



Scheme 47

The enantioselective synthesis of the alkaloid (+)-meloscine was achieved by constructing the last ring through RCM reaction catalyzed by **2** (Scheme 48).[125]



Scheme 48

4. CONCLUDING REMARKS

The ring-closing metathesis reactions of nitrogen-containing compounds have been used intensively for the synthesis of a variety of six-membered nitrogen heterocycles, clearly establishing that this reaction has become a standard synthetic methodology in the arsenal of heterocyclic chemists. The tetrahydropyridines and related derivatives prepared by RCM reactions are excellent precursors for the synthesis of saturated nitrogen heterocycles bearing a resemblance either to natural products or bioactive molecules. The synthetic potential of the intermediates generated through this chemistry has been further explored successfully. Nevertheless, although tremendous advances have been achieved in the field of RCM reactions, the applications of such processes to heterocyclic chemistry will continue to grow.

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REFERENCES

1. For Nobel Lectures see: R. H. Grubs, *Angew. Chem. Int. Ed.,* 2006, **45**, 3760 and *Adv. Synth. Cat.,* 2007, **349**, 34; R. R. Schrock, *Angew. Chem. Int. Ed.,* 2006, **45**, 3748 and *Adv. Synth. Cat.,* 2007, **349**, 41; Y. Chauvin, *Angew. Chem. Int. Ed.,* 2006, **45**, 3740 and *Adv. Synth. Cat.,* 2007, **349**, 27.
2. G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.,* 2010, **110**, 1746.
3. Y. Schrodi and R. L. Pederson, *Aldrichimica Acta,* 2007, **40**, 45.
4. L. Gulajski, M. Mauduit, and K. Grela, *Pure Appl. Chem.,* 2009, **81**, 2001.
5. C. Samojlowicz, M. Bieniek, and K. Grela, *Chem. Rev.,* 2009, **109**, 3708.
6. ‘Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysis’, ed by J. Cossy, S. Arseniyadis, and C. Meyer, Wiley: New York, 2010.
7. A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, and A. R. Zhugralin, *Angew. Chem. Int. Ed.,* 2010, **49**, 34.
8. S. P. Nolan and H. Clavier, *Chem. Soc. Rev.,* 2010, **39**, 3305.
9. *Adv. Synth. Catal.* 2007, **349**, 1 (Several authors, Olefin Metathesis Special Issue).
10. R. H. Grubbs,‘Handbook of Metathesis’, Wiley-VCH: Weinheim, 2003; Vols. 1-3.
11. S. Kotha, M. Meshram, and A. Tiwari, *Chem. Soc. Rev.,* 2009, **38**, 2065.
12. A. M. Lozano-Vila, S. Monsaert, A. Bajek, and F. Verpoort, *Chem. Rev.,* 2010, **110**, 4865.
13. H. Mutlu, L. Montero de Espinosa, and M. A. R. Meier, *Chem. Soc. Rev.,* 2011, **40**, 1404.
14. R. H. Grubbs, *Tetrahedron,* 2004, **60**, 7117.
15. A. Fürstner, *Angew. Chem. Int. Ed.,* 2000, **39**, 3012.
16. M. Schuster and S. Blechert, *Angew. Chem. Int. Ed.,* 1997, **36**, 2036.
17. T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.,* 2001, **34**, 18.
18. R. H. Grubbs, S. J. Miller, and G. C. Fu, *Acc. Chem. Res.,* 1995, **28**, 446.
19. L. Yet, *Chem. Rev.,* 2000, **100**, 2963.
20. S. K. Chattopadhyay, S. Karmakar, T. Biswas, K. C. Majumdar, H. Rahaman, and B. Roy, *Tetrahedron,* 2007, **63**, 3919.
21. K. J. Ivin, *J. Mol. Cat. A: Chem.,* 1998, **133**, 1.
22. H. M. A. Hassan, *Chem. Commun.,* 2010, 9100.
23. K.-i. Takao and K.-i. Tadano, *Heterocycles,* 2010, **81**, 1603.
24. W. A. L. van Otterlo and C. B. de Koning, *Chem. Rev.,* 2009, **109**, 3743.
25. K. C. Majumdar, S. Muhuri, R. U. Islam, and B. Chattopadhyay, *Heterocycles,* 2009, **78**, 1109.

26. G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.,* 1992, **114**, 7324.

27. G. C. Fu, S. T. Nguyen, and R. H. Grubbs, *J. Am. Chem. Soc.,* 1993, **115**, 9856.

28. A. J. Vernall and A. D. Abell, *Aldrichimica Acta,* 2003, **36**, 93.

29. A. J. Phillips and A. D. Abell, *Aldrichimica Acta,* 1999, **32**, 75.

30. F.-X. Felpin and J. Lebreton, *Eur. J. Org. Chem.,* 2003, 3693.

31. J. S. Yadav, M. S. Reddy, P. P. Rao, and A. R. Prasad, *Synthesis,* 2006, 4005.

32. M. S. Reddy, M. Narender, and K. R. Rao, *Tetrahedron,* 2006, **63**, 331.

33. H. Ouchi, Y. Mihara, and H. Takahata, *J. Org. Chem.,* 2005, **70**, 5207.

34. C. Alegret, X. Ginesta, and A. Riera, *Eur. J. Org. Chem.,* 2008, 1789.

35. C. Ohara, R. Takahashi, T. Miyagawa, Y. Yoshimura, A. Kato, I. Adachi, and H. Takahata, *Bioorg. Med. Chem. Lett.,* 2008, **18**, 1810.

36. B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, and A. Silvani, *Tetrahedron Lett.,* 2005, **46**, 7121.

37. P. P. Saikia, G. Baishya, A. Goswami, and N. C. Barua, *Tetrahedron Lett.,* 2008, **49**, 6508.

38. A. Kamal, S. R. Vangala, N. V. Subba Reddy, and V. Santhosh Reddy, *Tetrahedron: Asymmetry,* 2009, **20**, 2589.

39. L. Banfi, G. Guanti, M. Paravidino, and R. Riva, *Org. Biomol. Chem.,* 2005, **3**, 1729.

40. A. K. Srivastava, S. K. Das, and G. Panda, *Tetrahedron,* 2009, **65**, 5322.

41. M. Venkataiah and N. W. Fadnavis, *Tetrahedron,* 2009, **65**, 6950.

42. M. Venkataiah, B. Venkateswara Rao, and N. W. Fadnavis, *Tetrahedron: Asymmetry,* 2009, **20**, 198.

43. S.-J. Pyun, K.-Y. Lee, C.-Y. Oh, J.-E. Joo, S.-H. Cheon, and W.-H. Ham, *Tetrahedron,* 2005, **61**, 1413.

44. L.-S. Li and S. C. Sinha, *Tetrahedron Lett.,* 2009, **50**, 2932.

45. R. Rengasamy, M. J. Curtis-Long, W. D. Seo, S. H. Jeong, I.-Y. Jeong, and K. H. Park, *J. Org. Chem.,* 2008, **73**, 2898.

46. Z.-F. Xie, Z. Chai, G. Zhao, and J.-D. Wang, *Synthesis,* 2008, 3805.

47. T. M. Shaikh and A. Sudalai, *Tetrahedron: Asymmetry,* 2009, **20**, 2287.

48. D. Gagnon, S. Lauzon, C. Godbout, and C. Spino, *Org. Lett.,* 2005, **7**, 4769.

49. L. Boisvert, F. Beaumier, and C. Spino, *Can. J. Chem.,* 2006, **84**, 1290.

50. S. Lauzon, F. Tremblay, D. Gagnon, C. Godbout, C. Chabot, C. Mercier-Shanks, S. Perreault, H. DeSeve, and C. Spino, *J. Org. Chem.,* 2008, **73**, 6239.

51. F. A. Davis, Y. Zhang, and D. Li, *Tetrahedron Lett.,* 2007, **48**, 7838.

52. F. A. Davis and Y. Zhang, *Tetrahedron Lett.,* 2009, **50**, 5205.

53. O. Pavlyuk, H. Teller, and M. C. McMills, *Tetrahedron Lett.,* 2009, **50**, 2716.

54. T. S. Cooper, A. S. Larigo, P. Laurent, C. J. Moody, and A. K. Takle, *Org. Biomol. Chem.,* 2005, **3**, 1252.

55. I. S. Kim, Y. J. Ji, and Y. H. Jung, *Tetrahedron Lett.,* 2006, **47**, 7289.

56. I. S. Kim, J. S. Oh, O. P. Zee, and Y. H. Jung, *Tetrahedron,* 2007, **63**, 2622.

57. M. Pena-Lopez, M. M. Martinez, L. A. Sarandeses, and J. P. Sestelo, *Org. Lett.,* 2010, **12**, 852.

58. A. Fürstner and J. Ackerstaff, *Chem. Commun.,* 2008, 2870.

59. H. Nomura and C. J. Richards, *Org. Lett.,* 2009, **11**, 2892.

60. M. L. Bennasar, T. Roca, and D. Garcia-Diaz, *Synlett,* 2008, 1487.

61. M. L. Bennasar, T. Roca, and D. Garcia-Diaz, *J. Org. Chem.,* 2008, **73**, 9033.

62. F. M. Sabbatini, R. Di Fabio, C. Griffante, G. Pentassuglia, L. Zonzini, S. Melotto, G. Alvaro, A. M. Capelli, L. Pippo, E. Perdona, Y. St. Denis, S. Costa, and M. Corsi, *Bioorg. Med. Chem. Lett.,* 2010, **20**, 623.

63. S. K. Chattopadhyay, T. Biswas, and T. Biswas, *Tetrahedron Lett.,* 2008, **49**, 1365.

64. S. K. Chattopadhyay, K. Sarkar, L. Thander, and S. P. Roy, *Tetrahedron Lett.,* 2007, **48**, 6113.

65. H. Takahata, Y. Suto, E. Kato, Y. Yoshimura, and H. Ouchi, *Adv. Synth. Catal.,* 2007, **349**, 685.

66. T. Ayad, Y. Genisson, and M. Baltas, *Org. Biomol. Chem.,* 2005, **3**, 2626.

67. D. D. Dhavale, S. M. Jachak, N. P. Karche, and C. Trombini, *Synlett,* 2004, 1549.

68. A. Boto, Y. De Leon, J. A. Gallardo, and R. Hernandez, *Eur. J. Org. Chem.,* 2005, 3461.

69. A. K. Ghosh, G. Schiltz, R. S. Perali, S. Leshchenko, S. Kay, D. E. Walters, Y. Koh, K. Maeda, and H. Mitsuya, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 1869.

70. H. Bittermann, F. Boeckler, J. Einsiedel, and P. Gmeiner, *Chem.Eur. J.,* 2006, **12**, 6315.

71. S. K. Ghosh, C. Ko, J. Liu, J. Wang, and R. P. Hsung, *Tetrahedron,* 2006, **62**, 10485.

72. A. F. Gasiecki, J. L. Cross, R. F. Henry, V. Gracias, and S. W. Djuric, *Tetrahedron Lett.,* 2008, **49**, 6286.

73. J. H. Lee, S. Shin, J. Kang, and S.-G. Lee, *J. Org. Chem.,* 2007, **72**, 7443.

74. I. D. Jenkins, F. Lacrampe, J. Ripper, L. Alcaraz, P. Van Le, G. Nikolakopoulos, P. de Almeida Leone, R. H. White, and R. J. Quinn, *J. Org. Chem.,* 2009, **74**, 1304.

75. A. Niida, S. Oishi, Y. Sasaki, M. Mizumoto, H. Tamamura, N. Fujii, and A. Otaka, *Tetrahedron Lett.,* 2005, **46**, 4183.

76. D. Bensa, I. Coldham, P. Feinaeugle, R. B. Pathak, and R. J. Butlin, *Org. Biomol. Chem.,* 2008, **6**, 1410.

77. A. Niida, H. Tanigaki, E. Inokuchi, Y. Sasaki, S. Oishi, H. Ohno, H. Tamamura, Z. Wang, S. C. Peiper, K. Kitaura, A. Otaka, and N. Fujii, *J. Org. Chem.,* 2006, **71**, 3942.

78. A. Niida, M. Mizumoto, T. Narumi, E. Inokuchi, S. Oishi, H. Ohno, A. Otaka, K. Kitaura, and N. Fujii, *J. Org. Chem.,* 2006, **71**, 4118.

79. G. Lesma, B. Danieli, A. Sacchetti, and A. Silvani, *J. Org. Chem.,* 2006, **71**, 3317.

80. K. Takahashi, H. Nakano, and R. Fujita, *Tetrahedron Lett.,* 2005, **46**, 8927.

81. T. P. Ribelin, A. S. Judd, I. Akritopoulou-Zanze, R. F. Henry, J. L. Cross, D. N. Whittern, and S. W. Djuric, *Org. Lett.,* 2007, **9**, 5119.

82. J. Minville, J. Poulin, C. Dufresne, and C. F. Sturino, *Tetrahedron Lett.,* 2008, **49**, 3677.

83. S. Ghosh and J. Shashidhar, *Tetrahedron Lett.,* 2009, **50**, 1177.

84. J. Ceccon, A. E. Greene, and J.-F. Poisson, *Org. Lett.,* 2006, **8**, 4739.

85. J. D. Sunderhaus, C. Dockendorff, and S. F. Martin, *Org. Lett.,* 2007, **9**, 4223.

86. T. Muramatsu, S. Yamashita, Y. Nakamura, M. Suzuki, N. Mase, H. Yoda, and K. Takabe, *Tetrahedron Lett.,* 2007, **48**, 8956.

87. V. Zambrano, G. Rassu, A. Roggio, L. Pinna, F. Zanardi, C. Curti, G. Casiraghi, and L. Battistini, *Org. Biomol. Chem.,* 2010, **8**, 1725.

88. (a) N. Langlois, B. K. Le Nguyen, P. Retailleau, C. Tarnus, and E. Salomon, *Tetrahedron: Asymmetry,* 2006, **17**, 53; (b) G. Lesma, A. Colombo, A. Sacchetti, and A. Silvani, *J. Org. Chem.,* 2009, **74**, 590.

89. G. Lesma, A. Colombo, N. Landoni, A. Sacchetti, and A. Silvani, *Tetrahedron: Asymmetry,* 2007, **18**, 1948.

90. A. G. H. Wee, G.-J. Fan, and H. M. Bayirinoba, *J. Org. Chem.,* 2009, **74**, 8261.

91. F. Mo, F. Li, D. Qiu, and J. Wang, *Tetrahedron,* 2010, **66**, 1274.

92. R. Martin, C. Murruzzu, M. A. Pericas, and A. Riera, *J. Org. Chem.,* 2005, **70**, 2325.

93. M. S. M. Pearson, R. O. Saad, T. Dintinger, H. Amri, M. Mathe-Allainmat, and J. Lebreton, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 3262.

94. K. Maki, M. Kanai, and M. Shibasaki, *Tetrahedron,* 2007, **63**, 4250.

95. S. Chandrasekhar and B. Tiwari, *Tetrahedron: Asymmetry,* 2009, **20**, 1924.

96. N. Dieltiens, D. D. Claeys, V. V. Zhdankin, V. N. Nemykin, B. Allaert, F. Verpoort, and C. V. Stevens, *Eur. J. Org. Chem.,* 2006, 2649.

97. K. Schulz, M. Watzke, K. Johannes, P. Ullrich, and J. Martens, *Synthesis,* 2009, 665.

98. J. G. Sosnicki, *Tetrahedron Lett.,* 2006, **47**, 6809.

99. S.-S. P. Chou, C.-F. Liang, T.-M. Lee, and C.-F. Liu, *Tetrahedron,* 2007, **63**, 8267.

100. J. G. Sosnicki, *Synlett,* 2009, 2508.

101. N. R. Norcross, J. P. Melbardis, M. F. Solera, M. A. Sephton, C. Kilner, L. N. Zakharov, P. C. Astles, S. L. Warriner, and P. R. Blakemore, *J. Org. Chem.,* 2008, **73**, 7939.

102. N. Dieltiens, D. D. Claeys, B. Allaert, F. Verpoort, and C. V. Stevens, *Chem. Commun.,* 2005, 4477.

103. N. Toyooka, S. Kobayashi, D. Zhou, H. Tsuneki, T. Wada, H. Sakai, H. Nemoto, T. Sasaoka, H. M. Garraffo, T. F. Spande, and J. W. Daly, *Bioorg. Med. Chem. Lett.,* 2007, **17**, 5872.

104. B. Le Bourdonnec, A. J. Goodman, M. Michaut, H.-F. Ye, T. M. Graczyk, S. Belanger, T. Herbertz, G.

P. A. Yap, R. N. DeHaven, and R. E. Dolle, *J. Med. Chem.,* 2006, **49**, 7278.

105. Y. Nishikawa, M. Kitajima, and H. Takayama, *Org. Lett.,* 2008, **10**, 1987.
106. Y. Nishikawa, M. Kitajima, N. Kogure, and H. Takayama, *Tetrahedron,* 2009, **65**, 1608.
107. N. Kumari and Y. D. Vankar, *Org. Biomol. Chem.,* 2009, **7**, 2104.
108. G. Cheng, X. Wang, D. Su, H. Liu, F. Liu, and Y. Hu, *J. Org. Chem.,* 2010, **75**, 1911.
109. S. Fustero, N. Mateu, L. Albert, and J. L. Acena, *J. Org. Chem.,* 2009, **74**, 4429.
110. R. W. Bates, J. A. Nemeth, and R. H. Snell, *Synthesis,* 2008, 1033.
111. A. Adrien, H.-J. Gais, F. Koehler, J. Runsink, and G. Raabe, *Org. Lett.,* 2007, **9**, 2155.
112. B. G. Reddy and Y. D. Vankar, *Angew. Chem. Int. Ed.,* 2005, **44**, 2001.
113. A. Kumar, G. K. Rawal, and Y. D. Vankar, *Tetrahedron,* 2008, **64**, 2379.
114. S. Ghosh, J. Shashidhar, and S. K. Dutta, *Tetrahedron Lett.,* 2006, **47**, 6041.
115. L. Moisan, P. Thuery, M. Nicolas, E. Doris, and B. Rousseau, *Angew. Chem. Int. Ed.,* 2006, **45**, 5334.
116. S. Liu, Y. Fan, X. Peng, W. Wang, W. Hua, H. Akber, and L. Liao, *Tetrahedron Lett.,* 2006, **47**, 7681.
117. P. Kim, L. Zhang, U. H. Manjunatha, R. Singh, S. Patel, J. Jiricek, T. H. Keller, H. I. Boshoff, C. E. Barry, III, and C. S. Dowd, *J. Med. Chem.,* 2009, **52**, 1317.
118. D. L. Wright, J. P. Schulte, and M. A. Page, *Org. Lett.,* 2000, **2**, 1847.
119. S. H. L. Verhelst, B. P. Martinez, M. S. M. Timmer, G. Lodder, G. A. Van der Marel, H. S. Overkleeft, and J. H. Van Boom, *J. Org. Chem.,* 2003, **68**, 9598.
120. T. L. Suyama and W. H. Gerwick, *Org. Lett.,* 2006, **8**, 4541.
121. M. Nath, R. Mukhopadhyay, and A. Bhattacharjya, *Org. Lett.,* 2006, **8**, 317.
122. A. J. Murray and P. J. Parsons, *Synlett,* 2006, 1443.
123. A. J. Murray and P. J. Parsons, and P. Hitchcock, *Tetrahedron,* 2007, **63**, 6485.
124. J. Louvel, C. Botuha, F. Chemla, E. Demont, F. Ferreira, and A. Perez-Luna, *Eur. J. Org. Chem.,* 2010, 2921.
125. P. Selig and T. Bach, *Angew. Chem. Int. Ed.,* 2008, **47**, 5082.

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